ine. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported. NRTIs have also been associated with mitochondrial dysfunction manifesting as abnormal behaviour, anaemia, convulsions, hyperlipasaemia, hypertonia, and neutropenia. Elevated creatine phosphokinase, myalgia, myositis, and rarely rhabdomyolysis have been reported, particularly when nucleoside analogues have been given with HIV-protease inhibitors. Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy. For further information on adverse effects associated with NRTIs see Zidovudine, p.914.

### Precautions

Treatment with emtricitabine should be stopped if there is a rapid increase in aminotransferase concentrations, progressive hepatomegaly or steatosis, or metabolic or lactic acidosis of unknown aetiology. Emtricitabine should be given with caution to patients with hepatomegaly or other risk factors for liver disease. Patients co-infected with chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events; treatment should be interrupted or stopped if there is evidence of exacerbation of liver disease. It is recommended that all patients should be tested for the presence of hepatitis B infection before treatment is begun, and that patients co-infected with HIV and hepatitis B should be monitored for several months after stopping treatment with emtricitabine for signs of exacerbations of hepatitis. Emtricitabine should be used with caution and doses adjusted in patients with renal impairment.

### Interactions

Caution should be exercised when emtricitabine is given with other drugs eliminated by active tubular secretion as competition for the elimination pathway may increase the serum concentrations of either drug.

### Antiviral Action

Emtricitabine is converted intracellularly in stages to the triphosphate. This triphosphate halts the DNA synthesis of HIV through competitive inhibition of reverse transcriptase. Emtricitabine-resistant strains of HIV have been identified and cross-resistance to other nucleoside reverse transcriptase inhibitors may occur.

### Pharmacokinetics

Emtricitabine is rapidly and extensively absorbed from the gastrointestinal tract after oral doses, with peak plasma concentrations occurring after 1 to 2 hours. Bioavailability is reported to be 93% for the capsules. Binding to plasma proteins is reported to be less than 4%. The plasma elimination half-life is about 10 hours. Emtricitabine is metabolised to a limited degree, but is excreted largely unchanged in the urine and to a lesser extent in the faeces. It is partially removed by haemodialysis.

### Uses and Administration

Emtricitabine is a nucleoside reverse transcriptase inhibitor related to cytosine with antiviral activity against HIV-1 and hepatitis B virus. It is used in the treatment of HIV infection and AIDS (p.856). Viral resistance emerges rapidly when emtricitabine is used alone, and it is therefore used with other antiretrovirals.

Emtricitabine is given orally once daily as capsules in a usual adult dose of 200 mg or 240 mg as oral solution.

For details of doses in infants, children, and adolescents, see below.

For details of doses of emtricitabine to be used in patients with renal impairment, see below.

Fixed-dose combination products have been developed in order to improve patient adherence and avoid monotherapy, thereby decreasing the risk of acquired drug resistance. Products containing emtricitabine in combination with tenofovir, and with efavirenz plus tenofovir are available in some countries.

◊ Reviews.


1. Dando TM, Wagstaff AJ. Emtricitabine/tenofovir disoproxil fumarate. *Drugs* 2004; **64:** 2075–82.
2. Modrzejewski KA, Herman RA. Emtricitabine: a once-daily nucleoside reverse transcriptase inhibitor. *Ann Pharmacother* 2004; **38:** 1006–14.
3. Frampton JE, Perry CM. Emtricitabine: a review of its use in the management of HIV infection. *Drugs* 2005; **65:** 1427–48.
4. Saag MS. Emtricitabine, a new antiretroviral agent with activity against HIV and hepatitis B virus. *Clin Infect Dis* 2006; **42:** 126–31.


**Administration in children.** For the treatment of HIV infection in infants, children, and adolescents emtricitabine is given with other antiretroviral drugs. Doses, given once daily, are based on body-weight:

- in infants up to 3 months of age the *oral solution* is given in a dose of 3 mg/kg daily
- in infants, children, and adolescents over 3 months of age the oral solution is given in a dose of 6 mg/kg daily to a maximum daily dose of 240 mg
- the *capsules* may be given to children and adolescents weighing more then 33 kg in the usual adult dose of 200 mg daily.

**Administration in renal impairment.** Doses of emtricitabine should be reduced in patients with renal impairment, according to the patient's creatinine clearance (CC):

- CC at least 50 mL/minute: usual adult doses (as capsules or solution)
- CC 30 to 49 mL/minute: 200 mg every 48 hours (capsules) or 120 mg every 24 hours (oral solution)
- CC 15 to 29 mL/minute: 200 mg every 72 hours (capsules) or 80 mg every 24 hours (oral solution)
- CC less than 15 mL/minute: 200 mg every 96 hours (capsules) or 60 mg every 24 hours (oral solution)

### Preparations

**Proprietary Preparations** (details are given in Part 3)
***Arg.:*** Emtriva; ***Austral.:*** Emtriva; ***Belg.:*** Emtriva; ***Cz.:*** Emtriva; ***Denm.:*** Emtriva; ***Fin.:*** Emtriva; ***Fr.:*** Emtriva; ***Ger.:*** Emtriva; ***Gr.:*** Emtriva; ***Hung.:*** Emtriva; ***Irl.:*** Emtriva; ***Ital.:*** Emtriva; ***Mex.:*** Emtriva; ***Neth.:*** Emtriva; ***Norw.:*** Emtriva; ***NZ:*** Emtriva; ***Pol.:*** Emtriva; ***Port.:*** Emtriva; ***Spain:*** Emtriva; ***Swed.:*** Emtriva; ***Switz.:*** Emtriva; ***UK:*** Emtriva; ***USA:*** Emtriva.

**Multi-ingredient:** ***Arg.:*** Truvada; ***Austral.:*** Truvada; ***Cz.:*** Truvada; ***Fin.:*** Truvada; ***Fr.:*** Truvada; ***Ger.:*** Truvada; ***Gr.:*** Truvada; ***Irl.:*** Truvada; ***Ital.:*** Truvada; ***Mex.:*** Truvada; ***Neth.:*** Truvada; ***NZ:*** Truvada; ***Port.:*** Truvada; ***Spain:*** Truvada; ***Swed.:*** Truvada; ***UK:*** Atripla; Truvada; ***USA:*** Atripla; Truvada.

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## Enfuvirtide *(BAN, USAN, rINN)*

DP-178; Enfuvirtida; Enfuvirtidum; Pentafusida; Pentafuside; T-20.

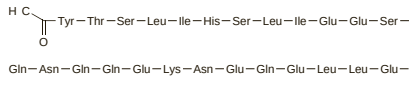
Энфувиртид

$C_{204}H_{301}N_{51}O_{64}$ = 4491.9.

*CAS — 159519-65-0.*

*ATC — J05AX07.*

*ATC Vet — QJ05AX07.*




### Adverse Effects

The most common adverse effects associated with antiretroviral regimens containing enfuvirtide are local injection site reactions with resultant pain, erythema, induration, nodules and cysts, pruritus, and ecchymosis. These reactions have been reported to occur in 98% of patients, but only a small minority needed to stop therapy. Other very common adverse effects include nausea, diarrhoea, weight loss, and peripheral neuropathy. Anorexia, abdominal pain, constipation, pancreatitis, myalgia, weakness or loss of strength, lymphadenopathy, insomnia, depression, 'flu-like' illness, sinusitis, and conjunctivitis are also common. An increased incidence of some bacterial infections, in particular of pneumonia, has occurred in patients receiving enfuvirtide. Hypersensitivity reactions have occurred in about 1% of patients. Other adverse effects have included anxiety, hyperglycaemia, hypertriglyceridaemia, and eosinophilia.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy in HIV-infected patients with severe immune deficiency. Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy.

◊ References.


1. Maggi P, *et al.* Cutaneous injection site reactions to long-term therapy with enfuvirtide. *J Antimicrob Chemother* 2004; **53:** 678–81.


### Precautions

Enfuvirtide should be stopped immediately and should not be restarted in patients who develop signs of a systemic hypersensitivity reaction. An increased incidence of some bacterial infections, in particular of pneumonia, has been seen and patients receiving enfuvirtide should be closely monitored for signs of pneumonia. UK licensed product information recommends that enfuvirtide be used with caution in patients with hepatic impairment and in those with moderate to severe renal impairment. Patients co-infected with chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events.

### Antiviral Action

Enfuvirtide is an HIV fusion inhibitor that interferes with entry of HIV into cells by binding to the gp41 subunit of the viral envelope glycoprotein, thereby inhibiting fusion of viral and cellular membranes. Strains of HIV with reduced susceptibility to enfuvirtide have been isolated in patients receiving the drug but, owing to the different mode of action of enfuvirtide and the fact that it does not require intracellular activation for its activity, cross-resistance with other antiretrovirals may occur less frequently.

**Resistance.** References to the development of resistance to enfuvirtide.


1. Greenberg ML, Cammack N. Resistance to enfuvirtide, the first HIV fusion inhibitor. *J Antimicrob Chemother* 2004; **54:** 333–40.


### Pharmacokinetics

Enfuvirtide is absorbed after subcutaneous injection with a mean absolute bioavailability of 84%. It is 92% bound to plasma proteins. Enfuvirtide is a peptide and is metabolised by hydrolysis; it does not inhibit cytochrome P450 isoenzymes. The elimination half-life is 3.8 hours after subcutaneous use, although elimination pathways have yet to be identified.

◊ References.


1. Patel IH, *et al.* Pharmacokinetics, pharmacodynamics and drug interaction potential of enfuvirtide. *Clin Pharmacokinet* 2005; **44:** 175–86.
2. Zhang X, *et al.* Population pharmacokinetics of enfuvirtide in HIV-1-infected pediatric patients over 48 weeks of treatment. *J Clin Pharmacol* 2007; **47:** 510–17.


### Uses and Administration

Enfuvirtide is a synthetic 36-amino acid peptide that blocks HIV cell fusion and viral entry. It is used with other antiretrovirals for combination therapy of HIV infection and AIDS. Enfuvirtide is given by subcutaneous injection into the upper arm, anterior thigh, or abdomen in a usual dose of 90 mg twice daily. Each injection should be given at a different site from the preceding one. For details of doses in children and adolescents, see below.

◊ References.


1. Lalezari JP, *et al.* Enfuvirtide, an HIV-1 fusion inhibitor, for drug-resistant HIV infection in North and South America. *N Engl J Med* 2003; **348:** 2175–85. Correction. *ibid.*; **349:** 1100.
2. Duffalo ML, James CW. Enfuvirtide: a novel agent for the treatment of HIV-1 infection. *Ann Pharmacother* 2003; **37:** 1448–56.
3. Oldfield V, *et al.* Enfuvirtide: a review of its use in the management of HIV infection. *Drugs* 2005; **65:** 1139–60.

4. Reynes J, *et al.* TORO: ninety-six-week virologic and immunologic response and safety evaluation of enfuvirtide with an optimized background of antiretrovirals. *AIDS Patient Care STDS* 2007; **21:** 533–43.
5. Wiznia A, *et al.* T20-310 Study Group. Safety and efficacy of enfuvirtide for 48 weeks as part of an optimized antiretroviral regimen in pediatric human immunodeficiency virus 1-infected patients. *Pediatr Infect Dis J* 2007; **26:** 799–805.
6. Rockstroh J, *et al.* Adherence to enfuvirtide and its impact on treatment efficacy. *AIDS Res Hum Retroviruses* 2008; **24:** 141–8.
7. Saberi P, *et al.* Immunologic benefits of enfuvirtide in patients enrolled in a drug assistance program. *Ann Pharmacother* 2008; **42:** 621–6.

**Administration in children.** For the treatment of HIV infection, enfuvirtide may be given to children 6 to 16 years of age by subcutaneous injection into the upper arm, anterior thigh, or abdomen in a dose of 2 mg/kg twice daily (to a maximum of 90 mg twice daily). Each injection should be given at a different site from the preceding one.

### Preparations

**Proprietary Preparations** (details are given in Part 3)
***Arg.:*** Fuzeon; ***Austral.:*** Fuzeon; ***Belg.:*** Fuzeon; ***Braz.:*** Fuzeon; ***Canad.:*** Fuzeon; ***Chile:*** Fuzeon; ***Cz.:*** Fuzeon; ***Denm.:*** Fuzeon; ***Fin.:*** Fuzeon; ***Fr.:*** Fuzeon; ***Ger.:*** Fuzeon; ***Gr.:*** Fuzeon; ***Hung.:*** Fuzeon; ***Irl.:*** Fuzeon; ***Israel:*** Fuzeon; ***Ital.:*** Fuzeon; ***Mex.:*** Fuzeon; ***Neth.:*** Fuzeon; ***Norw.:*** Fuzeon; ***NZ:*** Fuzeon; ***Pol.:*** Fuzeon; ***Port.:*** Fuzeon; ***Spain:*** Fuzeon; ***Swed.:*** Fuzeon; ***Switz.:*** Fuzeon; ***Thai.:*** Fuzeon; ***UK:*** Fuzeon; ***USA:*** Fuzeon.

## Entecavir *(USAN, rINN)*

BMS-200475-01; Entécavir; Entecavirum; SQ-34676. 9-[(1*S*,3*R*,4*S*)-4-Hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]guanine monohydrate.

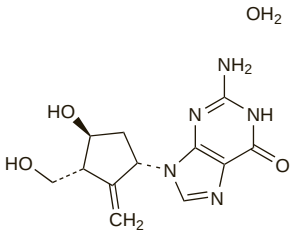
Энтекавир

$C_{12}H_{15}N_5O_3,H_2O$ = 295.3.

*CAS — 142217-69-4 (anhydrous entecavir); 209216-23-9 (entecavir monohydrate).*

*ATC — J05AF10.*

*ATC Vet — QJ05AF10.*



### Adverse Effects

The most common adverse effects of entecavir have been headache, fatigue, dizziness, and nausea. Other adverse effects include diarrhoea, dyspepsia, insomnia, somnolence, and vomiting.

Raised liver enzyme concentrations may occur and exacerbation of hepatitis has been reported after stopping treatment with entecavir. Lactic acidosis, usually associated with severe hepatomegaly and steatosis, has been associated with treatment with nucleoside analogues alone or with antiretrovirals (see Zidovudine, p.914).

Entecavir is carcinogenic in *rodents*, but a relationship with human cancer has not been established.

### Precautions

Entecavir should be withdrawn if there is a rapid increase in aminotransferase concentrations, progressive hepatomegaly or steatosis, or metabolic or lactic acidosis of unknown aetiology. Entecavir should be given with caution to patients with hepatomegaly or other risk factors for liver disease. Careful differentiation should be made between patients whose liver enzyme concentrations become elevated due to response to treatment and those in whom it is indicative of toxicity. Exacerbation of hepatitis B has been reported both during and after stopping treatment with entecavir. Hepatic function should be monitored closely while on treatment and for several months after treatment is stopped. Dosage reduction may be necessary in patients with renal impairment.

Limited clinical experience suggests there is a potential for HIV to develop resistance to NRTIs if entecavir is used to treat chronic hepatitis B virus infection in patients with undiagnosed or untreated HIV infection. Treatment with entecavir is not recommended for co-infected patients who are not also receiving HAART. US licensed product information recommends that all patients be tested for HIV antibodies before starting treatment with entecavir.

**HIV-infected patients.** It was initially thought that entecavir did not inhibit replication of HIV-1 at clinically relevant doses. However, a small consistent decrease in HIV-1 RNA was noted in 3 patients with HIV-1 and hepatitis B virus co-infection being treated with entecavir monotherapy.[1] In 1 of these patients, an HIV variant containing the M184V resistance substitution was found. Subsequent *in vitro* analyses showed that HIV-1 strains containing M184V were resistant to entecavir.

1. McMahon MA, *et al.* The HBV drug entecavir—effects on HIV-1 replication and resistance. *N Engl J Med* 2007; **356:** 2614–21.

### Interactions

Caution should be exercised when entecavir is given with other drugs eliminated by active tubular secretion as competition for the elimination pathway may increase the serum concentrations of either drug.

### Antiviral Action

Entecavir is phosphorylated intracellularly to the active triphosphate form which competes with deoxyguanosine triphosphate, the natural substrate of hepatitis B virus reverse transcriptase, thereby inhibiting every stage of the enzyme's activity.

Although initially thought to be inactive against HIV at clinically relevant doses, entecavir may have sufficient action to result in the selection of resistant HIV variants (see HIV-infected Patients, under Precautions, above).

### Pharmacokinetics

Entecavir is rapidly absorbed from the gastrointestinal tract after oral doses. Peak plasma concentrations occur 30 to 90 minutes after an oral dose and steady state concentrations after 6 to 10 days of treatment. Absorption is both delayed and reduced by food; this is not considered to be clinically relevant in nucleoside treatment-naive patients but may affect efficacy in lamivudine-refractory patients in whom entecavir should be taken on an empty stomach. Bioavailability of the tablet formulation is equal to that of the oral solution and they may be given interchangeably. Binding of entecavir to plasma proteins is about 13% *in vitro*. Entecavir is not metabolised by the cytochrome P450 system. It is mainly eliminated by the kidneys by glomerular filtration and active tubular secretion, with a terminal elimination half-life of 128 to 149 hours. Small amounts of glucuronide and sulfate conjugates are formed. Entecavir is partially removed by haemodialysis.

### Uses and Administration

Entecavir is a nucleoside reverse transcriptase inhibitor, structurally related to guanosine with selective antiviral activity against hepatitis B virus. It is used for the treatment of chronic hepatitis B (p.851) in adults with compensated liver disease with evidence of active viral replication, persistently elevated liver enzyme values, and histologically active disease, including those resistant to lamivudine. The usual oral dose of entecavir in nucleoside treatment-naive patients is 500 micrograms once daily, either with or without food. An oral dose of 1 mg once daily on an empty stomach should be used in patients with a history of hepatitis B viraemia during lamivudine therapy or with known resistance to lamivudine. For details of reduced doses to be used in patients with renal impairment, see below.

◊ Reviews.

1. Sims KA, Woodland AM. Entecavir: a new nucleoside analog for the treatment of chronic hepatitis B infection. *Pharmacotherapy* 2006; **26:** 1745–57.
2. Robinson DM, *et al.* Entecavir: a review of its use in chronic hepatitis B. *Drugs* 2006; **66:** 1605–22.
3. Matthews SJ. Entecavir for the treatment of chronic hepatitis B virus infection. *Clin Ther* 2006; **28:** 184–203.

**Administration in renal impairment.** Doses of entecavir should be reduced in patients with renal impairment according to creatinine clearance (CC) as follows:

- CC 30 to 49 mL/minute: 250 micrograms once daily or 500 micrograms every 48 hours in nucleoside treatment-naive patients; 500 micrograms once daily in lamivudine-refractory patients
- CC 10 to 29 mL/minute: 150 micrograms once daily or 500 micrograms every 72 hours in nucleoside treatment-naive patients; 300 micrograms once daily or 500 micrograms every 48 hours in lamivudine-refractory patients
- CC less than 10 mL/minute (and patients on haemodialysis or continuous ambulatory peritoneal dialysis): 50 micrograms once daily or 500 micrograms every 5 to 7 days in nucleoside treatment-naive patients; 100 micrograms once daily or 500 micrograms every 72 hours in lamivudine-refractory patients

Patients receiving haemodialysis should receive the appropriate dose after each dialysis session.

### Preparations

**Proprietary Preparations** (details are given in Part 3)
***Arg.:*** Baraclude; ***Austral.:*** Baraclude; ***Cz.:*** Baraclude; ***Fr.:*** Baraclude; ***Gr.:*** Baraclude; ***Hung.:*** Baraclude; ***Indon.:*** Baraclude; ***Malaysia:*** Baraclude; ***NZ:*** Baraclude; ***Philipp.:*** Baraclude; ***Port.:*** Baraclude; ***Singapore:*** Baraclude; ***UK:*** Baraclude; ***USA:*** Baraclude.

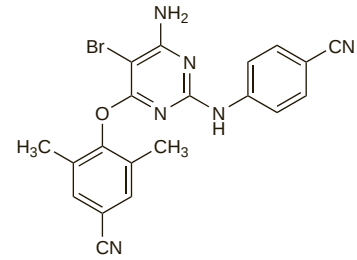
## Etravirine *(USAN, rINN)*

Etravirina; Étravirine; Etravirinum; R-165335; TMC-125. 4-[6-Amino-5-bromo-2-(4-cyanoanilino)pyrimidin-4-yloxy]-3,5-dimethylbenzonitrile.

Этравирин

$C_{20}H_{15}BrN_6O$ = 435.3.

*CAS — 269055-15-4.*



### Adverse Effects

The most common adverse effects associated with antiretroviral regimens containing etravirine are nausea and skin rash (usually mild to moderate) and generally appearing in the second week of treatment and resolving within 1 to 2 weeks. Severe skin reactions, including erythema multiforme and Stevens-Johnson syndrome, have occurred. Additional adverse events of moderate to severe intensity reported by at least 2% of patients receiving etravirine in clinical studies included gastrointestinal complaints (abdominal pain, diarrhoea, nausea, and vomiting), fatigue, headache, hypertension, and peripheral neuropathy. Raised liver enzyme values, glucose levels, and serum-cholesterol and -triglyceride concentrations have been reported.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including etravirine, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy, including etravirine.

### Precautions

Etravirine should be stopped if a severe skin rash develops. Patients co-infected with chronic hepatitis B or C have experienced worsening of hepatitis-related symptoms when treated with etravirine. Patients who have virologic failure on a NNRTI-containing regimen